Daptomycin – A New Antibiotic

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The burgeoning rates of antibiotic resistance among clinical isolates of gram positive bacteria and the upsurge in the rates of bacteremia caused by these organisms during recent times are causes of great concern [1].

The rising incidence of invasive infections by resistant staphylococcus aureus strains has created an urgent need for more potent anti staphylococcal agents [2].The growing crisis in antibiotic resistance has limited our ability to treat infections caused by resistant pathogens. Vancomycin remains the mainstay of therapy against several resistant gram positive organisms, but with the 20 fold increase in nosocomial infections caused by vancomycin resistant enterococci (VRE), there is a growing need for more potent antimicrobials to attack these resistant pathogens [3].

Daptomycin is the first antibacterial agent of a new class of antibiotics, the cyclic lipopeptides, derived from the natural fermentation of streptomyces rosesporus.

Daptomycin is safe and effective for the treatment of complicated skin and skin structure infections. Post hoc and subset analyses of data from two phase 3 trials suggest that daptomycin may result in faster clinical improvement and a shorter duration of therapy compared with treatment with penicillinase-resistant penicillins or vancomycin. A subsequent study on patients with skin and skin structure infections showed that daptomycin resulted in faster clinical improvement, shorter duration of intravenous antibiotic therapy, shorter antibiotic associated length of hospital stay and decreased total hospital costs compared with matched controls with vancomycin.

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History – The compound was originally discovered by researchers at Eli Lilly and company in the 1980's who designated the compound as LY 146032. Later it is marketed in September 2003. Further launches in Canada, various European countries and all over the world were expected in 2008 – 09 [4].

Mechanism of actions – daptomycin has a distinct mechanism of action, disrupting multiple aspects of bacterial cell membrane function. It binds to the membrane and cause rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death.

Daptomycin is only disrupting the membrane but not the cell wall. Therefore cell lysis does not take place with daptomycin.

Daptomycin is the most effective bactericidal antibiotic. The bactericidal activity of daptomycin is concentration dependent.

Microbiology – Daptomycin is effective against Gram positive bacteria only. It has proven in vitro activity against enterococci (including glycopeptides resistant Enterococci (GRE), staphylococci (including MRSA), streptococci & corynebacteria. Daptomycin is approved in unites States for skin & skin structure infections caused by Gram positive infections, Staphylococcus aureus bacteraemia and right sided S. aureus endocarditis [5].

Efficacy – Daptomycin has been shown to be not inferior to standard therapies (naficillin, oxacillin, flucloxacillin or vancomycin) in treatment of bacteremia and right sided endocarditis caused by staphylococcus aureus. A study carried out in USA on 53 patients of skin or soft tissue infections

suspected to have infection by MRSA. The result of treatment in these cases that were treated with Vancomycin versus Daptomycin was compared. It was observed that there was faster recovery in cases treated with daptomycin compared with vancomycin (4 days versus 7 days)[6].

Daptomycin is associated with poor outcome in cases with left sided endocarditis. It is inactivated by pulmonary surfactants for treatment of pneumonia. This drug is also not useful in prosthetic valve endocarditis or meningitis.

Dosage and presentation – The drug is given in the dosages of 4 mg/kg in skin and soft tissue infection intravenously once daily while in right sided endocarditis the dosage is 6 mg/kg IV once daily. The drug is given all 48 hours in patients with renal impairment with renal creatinine clearance <30ml/min. The drug is supplied as a sterile preservative free pale yellow to light brown lyophilized 500 mg and 350 mg cake that must be reconstituted with 0.9% saline prior to use. It is given as 30 minute infusion or 2 minute injection.

Adverse reactions – Daptomycin is associated with various adverse reactions[7]. These reactions are however seen only in 2 -3 % cases and are non fatal.

1) Cardiovascular System: - Hypotension (2.4%), oedema, cardiac failure, supraventricular tachycardia.
2) CNS:- Headache, Insomnia, dizziness, anxiety, confusion, vertigo, parasthesia
3) Dermatological: - Rash, pruritus, Eczema.
4) Endocrine:- Hypokalaemia, hyperglycaemia, hypomagnesemia, increased bicarbonates, electrolyte disturbances
5) Gasrointestinal:- Constipation, Nausea, diarrhea, vomiting, dyspepsia, abdominal pain, decreased apetite, stomatitis, flatulence
6) Hematological:- Anaemia, Leucocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased INR.
7) Hepatic:- Abnormal liver function tests, Jaundice
8) Musculoskeletal:- elevated creatinine kinase, limb pains, arthralgia, osteomylitis, muscle cramps
9) Renal: - Acute renal failure in 2.2%
10) Others: - Fever, dyspnoea, hypersensitivity

Precaution: - simultaneous use of statins should be avoided as there are reports of Myopathy and rhabdomyolysis occurring in patients simultaneously taking statins.

Gram positive organisms particularly S. aureus are responsible for lesions of skin & skin structure infections, bone and joint infections & right sided endocarditis. While vancomycin has long been the gold standard in such treatments, the emergence of vancomycin resistance demonstrated the need of alternative treatment. Daptomycin has shown promising results in such infections including those caused by MRSA & VRE. The novel mode of action, rapid bactericidal activity, once daily dosing, low potential for adverse reactions, well tolerance, low risk of spontaneous resistance has proved potentially therapeutic utility of this drug.

References: -

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